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(FILE 'HOME' ENTERED AT 09:46:42 ON 19 MAY 2000)

FILE 'MEDLINE, EMBASE, BIOSIS, CAPLUS' ENTERED AT 09:46:56 ON 19 MAY 2000

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L1           58 S ((LINDHOFER H.) OR (LINDHOFER H) OR (LINDHOFER, HORST) OR
(LI
L2         2128 S ((KOLB H.) OR (KOLB H.-J.) OR (KOLB H) OR (KOLB H-J) OR
(KOLB
L3          119 S ((ZEIDLER R.) OR (ZEIDLER R) OR (ZEIDLER, REINHARD) OR
(ZEIDL
L4           52 S ((BORNKAMM G.) OR (BORNKAMM G) OR (BORNKAMM, GEORG) OR
(BORNK
L5            0 S L1 AND L2 AND L3 AND L4
L6         3663 S BISPECIFIC OR TRISPECIFIC
L7           44 S L6 AND (L1 OR L2 OR L3 OR L4)
L8           25 DUP REM L7 (19 DUPLICATES REMOVED)
L9            5 S EX VIVO IMMUNIZATION
L10           2 DUP REM L9 (3 DUPLICATES REMOVED)
L11        8202 S PASSIVE IMMUNI?
L12           3 S L11 AND L6
L13           3 DUP REM L12 (0 DUPLICATES REMOVED)
L14        4045 S CELL? VACCIN?
L15          16 S L14 AND L6
L16           8 DUP REM L15 (8 DUPLICATES REMOVED)
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L16 ANSWER 1 OF 8 MEDLINE DUPLICATE 1

ACCESSION NUMBER: 1998192213 MEDLINE
DOCUMENT NUMBER: 98192213
TITLE: ***Bispecific*** antibodies increase T-cell stimulatory capacity in vitro of human autologous virus-modified tumor vaccine.
AUTHOR: Haas C; Strauss G; Moldenhauer G; Iorio R M; Schirrmacher V
CORPORATE SOURCE: Division of Cellular Immunology, German Cancer Research Center, Heidelberg.
SOURCE: CLINICAL CANCER RESEARCH, (1998 Mar) 4 (3) 721-30. Journal code: C2H. ISSN: 1078-0432.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199807
ENTRY WEEK: 19980705

AB The production and functional testing of two new ***bispecific*** (bs) hybrid antibodies [Abs; bs Ab hemagglutinin-neuraminidase (HN) x CD3 and bs Ab HN x CD28] designed for cancer vaccine modification are described. They allow distinct modifications of the human tumor ***cell*** ***vaccine*** ATV-NDV, an autologous tumor ***cell*** ***vaccine*** already modified by infection with Newcastle disease virus. The bs Abs use the viral HN molecule as a common foreign anchoring molecule for attachment to the tumor cells and allow the introduction of anti-CD3 or anti-CD28 T-cell-stimulatory molecules. The bs Abs attached to tumor target cells were able to cross-link CTL effector cells and up-regulate T-cell activation markers on autologous cancer patient-

derived
CD4 and CD8 T lymphocytes. This strategy of combining a ***cellular*** ***vaccine*** with a bs Ab is highly specific, quick, and economical and
has broad-range applications. Five ng or less of target cell-bound bs Ab HN x CD28 were effective at augmenting T-cell-mediated antitumor cytotoxicity.

L16 ANSWER 2 OF 8 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1999081280 MEDLINE
DOCUMENT NUMBER: 99081280
TITLE: Immunization with virus-modified tumor cells.
AUTHOR: Schirrmacher V; Ahlert T; Probstle T; Steiner H H; Herold-Mende C; Gerhards R; Hagmuller E; Steiner H H
CORPORATE SOURCE: Abteilung Zellulare Immunologie (G0100), Deutsches Krebsforschungszentrum, Heidelberg, Germany.
SOURCE: SEMINARS IN ONCOLOGY, (1998 Dec) 25 (6) 677-96. Ref: 66
Journal code: UN5. ISSN: 0093-7754.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199903
ENTRY WEEK: 19990303
AB Direct infection of tumor cells with viruses transfering protective or therapeutic genes-a frequently used procedure for production of tumor vaccines in human gene therapy-is often limited by the number of tumor cells that can reliably be infected, as well as by issues of selectivity and safety. In this review, we describe an efficient, selective, and safe way of infecting human tumor cells with a natural virus with interesting pleiotropic immune stimulatory properties, the avian paramyxovirus Newcastle disease virus (NDV). Advantages of this virus are its good cell-binding properties, its selective replication in tumor cell cytoplasm, which is independent of cell proliferation, and its relative safety. Most important for its use as an adjuvant in human cancer vaccine are its ability to introduce T-cell costimulatory activity, to prevent anergy induction, and to induce locally chemokines (eg, RANTES, IP-10) and
cytokines (eg, interferon alpha, beta [IFN-alpha, beta] and tumor necrosis
factor-alpha [TNFalpha]) that affect T-cell recruitment and activation. A further development consists of attachment-via NDV-derived hemagluttinin-neuraminidase (HN) membrane-anchoring molecules-of universal
defined ***bispecific*** reagents such as T-cell-activating anti-CD28 antibodies. Finally, we summarize the status of our clinical studies with the autologous virus modified live ***cell*** ***vaccine*** (ATV)-NDV.

L16 ANSWER 3 OF 8 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V. DUPLICATE 3
ACCESSION NUMBER: 1998404443 EMBASE
TITLE: Modification of cancer vaccines by virus infection and attachment of ***bispecific*** antibodies: An effective
alternative to somatic gene therapy.
AUTHOR: Schirrmacher V.; Haas C.
CORPORATE SOURCE: V. Schirrmacher, German Cancer Research Center, Division of

Cellular Immunology, Im Neuenheimer Feld 280, D-69120 Heidelberg, Germany. V.Schirrmacher@DKFZ-Heidelberg.de
SOURCE: Advances in Experimental Medicine and Biology, (1998) 451/- (251-257).
Refs: 43
ISSN: 0065-2598 CODEN: AEMBAP
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB A new type of cancer vaccine for therapeutic application in cancer patients is described. It consists of three components: 1) Autologous tumor cells, 2) Newcastle Disease Virus to be used for infection and 3) ***bispecific*** antibodies (bsAb) which attach to the viral hemagglutinin neuraminidase (HN) molecule on the infected tumor cells. A standardized procedure has been developed for generating virus infected human autologous tumor ***cell*** ***vaccines*** (ATV-NDV) which includes cell dissociation removal of leukocytes and cell debris, .gamma.-irradiation and cryopreservation. Modification with the non-virulent strain NDV-Ulster is performed within 30 minutes of co-incubation. Virus infection potentiated tumor vaccine T cell stimulatory capacity and created a vaccine which has been successful in mouse tumor models in preventing or delaying metastatic spread and improving survival. Virus potentiation required cell surface binding but not infection. Clinical phase II studies in patients with breast or ovarian cancer suggest clinical effectivity of postoperative vaccination with a high quality of ATV-NDV vaccine. Tumor cell number and viability turned out to be statistically significant parameters for quality and efficacy. While virus infection already increased immunogenicity of the tumor vaccine, further augmentation of T cell stimulatory capacity is achieved by attachment of specially designed ***bispecific*** antibodies bsAb HN x CD28 or bsAb HN x CD3. In human T cell stimulation studies in vitro, the bsAb-vaccine caused upregulation of early and late T cell activation markers, stimulated T cell proliferation and induced cell mediated cytotoxicity and tumor cytostasis in non-modified bystander tumor cells. This tumor vaccine modification procedure is highly specific, quick and economic and has broad range clinical applications.

L16 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:761947 CAPLUS
DOCUMENT NUMBER: 128:33765
TITLE: New antigen presenting cells, a process for preparing the same and their use as ***cellular*** ***vaccines***
INVENTOR(S): Chokri, Mohamed; Bartholeyns, Jacques; Romet-Lemonne, Jean Loup
PATENT ASSIGNEE(S): I.D.M. Immuno-Designed Molecules, Fr.
SOURCE: Eur. Pat. Appl., 18 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 808897	A1	19971126	EP 1996-401099	19960521
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
CA 2252505	AA	19971127	CA 1997-2252505	19970515
WO 9744441	A1	19971127	WO 1997-EP2703	19970515
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9729615	A1	19971209	AU 1997-29615	19970515
EP 925356	A1	19990630	EP 1997-924012	19970515
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2000503545	T2	20000328	JP 1997-541583	19970515
PRIORITY APPLN. INFO.:			EP 1996-401099	19960521
			WO 1997-EP2703	19970515

AB The invention relates to macrophages characterized in that they have the following properties: they present on their surface : antigen CD14 with a mean intensity of about 20 to about 200, antigen CD64 with a mean intensity of about 20 to about 200. They are substantially devoid of the surface antigens CD1a and CD1c. The presence and mean intensities resp. of CD14, CD64 and the absence of CD1a and CD1c being for instance detd. by immunofluorescence staining and flow cytometry anal. They present a phagocytosis property such as detd. by the following test: said phagocytosis capacity being evaluated by an uptake of formalin fixed yeast, for example, by culturing macrophages for 2 h, adding yeast in 1/10 macrophages/yeast ratio and incubating at 37.degree.C, 5% CO2 atmosphere for 2-3 h fixing by the May-Grunwald-Giems a (MGG) staining, and the percentage of phagocytic macrophages being quantified for instance by microscopic anal.. They have the property of stimulating the proliferation of allogenic lymphocytes such as detd. by the following test : allogenic primary mixed lymphocytes reaction (MLR) was carried out in 96-well microtiter plates by adding different nos. (2x103 to 2x105 in 100 .mu.l medium/well) of macrophages to 2x105 in 100 .mu.l medium/well of allogenic T cells purified from buffy coats and after 5 days incubation at 37.degree.C. Cell proliferation was assessed by a colorimetric method, such as the hydrolysis of tetrazolium salt WST-1 (Boekringer Mannheim, Germany), (slightly red) to formazan (dark Red).

L16 ANSWER 5 OF 8 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.DUPLICATE 4
ACCESSION NUMBER: 97315620 EMBASE
DOCUMENT NUMBER: 1997315620
TITLE: Effective introduction of T cell costimulatory molecules into virus modified tumor ***cell*** ***vaccines*** by modification with ***bispecific*** antibodies.
AUTHOR: Haas C.; Schirrmacher V.
CORPORATE SOURCE: Prof. V. Schirrmacher, Deutsches Krebsforschungszentrum, Abteilung 0710, Im Neuenheimer Feld 280, D-69120 Heidelberg, Germany

SOURCE: International Journal of Oncology, (1997) 11/5 (951-957).
Refs: 35
ISSN: 1019-6439 CODEN: IJONES
COUNTRY: Greece
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB This report describes the generation of ***bispecific*** antibodies which bind with one arm to virus modified tumor ***cell*** ***vaccines*** and introduce with the other arm anti-murine CD28 T cell costimulatory molecules. This is an effective alternative to somatic gene therapy strategies using genes coding for ligands of CD28 such as CD80 (B7-1) or CD86 (B7-2). While these B7 molecules interact not only with CD28 but also with CLTA-4, thereby generating a negative signal, agonistic anti CD28 antibodies only bind to CD28 and therefore deliver only positive costimulatory signals. The new ***bispecific*** antibody (bsAb) HN x CD28 allows the introduction of anti-CD28 antibodies into the tumor ***cell*** ***vaccine*** ATV-NDV, an autologous tumor ***cell*** ***vaccine*** already modified by infection with Newcastle Disease Virus (NDV). The bsAb HN x CD28 attaches with its anti-HN binding site to the NDV derived hemagglutinin-neuraminidase (HN) molecule which serves as a common foreign anchoring molecule in the vaccine. NDV infected tumor cells which were further modified with HN x CD28 on their cell surface (bs-vaccine), showed increased T cell stimulatory capacity in vitro. This was revealed by augmented proliferation as well as augmented CTL activity.
When syngeneic mice were injected with aggressive murine ESb lymphoma cells which were infected with NDV and further modified with the bsAb HN x CD28, delayed tumor development and prolonged survival was observed in comparison to respective controls.

L16 ANSWER 6 OF 8 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998209757 EMBASE
TITLE: The treatment of advanced renal cell carcinoma. Current and prospective views.
AUTHOR: Polyzos A.; Kostakis A.
CORPORATE SOURCE: A. Polyzos, Internal Med. 1st Propedeutic Dept., General Hospital 'Laikon', GR-115 27 Athens, Greece
SOURCE: Archives of Hellenic Medicine, (1997) 14/6 (609-618).
Refs: 55
ISSN: 1105-3992 CODEN: AEIAF7
COUNTRY: Greece
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 006 Internal Medicine
016 Cancer
028 Urology and Nephrology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: Greek

SUMMARY LANGUAGE: English; Greek

AB The natural history of renal cell carcinoma (RCC) is disappointing. Metastatic disease is present in 1/3 of patients on diagnosis while 30-40% will develop metastases subsequently. Nephrectomy can improve quality of life even in cases with metastasis, and if combined with metastasectomy may lead to prolongation of life. Radiotherapy has a limited role in the treatment of the primary tumor because of the tumor's relative resistance and the vicinity of the spinal cord. Radiotherapy may be applied as a palliative treatment for metatatic disease. Since RCC is usually advanced, systemic treatment is required but it is a chemoresistant tumor due mainly to the inherent multi- drug resistance mechanics. Chemotherapeutic responses to single agents and drug combinations are disappointing, with the exception of vinblastine and floxuridine which may include low rate responses. In addition, accordings to the new response criteria, RCC is considered hormonally refractory, since progrestins and other hormones can neither induce responses not improve the patient's quality of life. The best treatment responses have been achieved with biologic treatment, particularly with interferon-a (INF-.alpha.) and interleukin-2 (Il-2). RCC responds to IFN-a at a range of 15-17% with 2% complete responses. Median survival in responders in 7-18+ months (almost double that of comparative groups without treatment). INF-.alpha. may be administered subcutaneously, intramuscularly or intravenously, 3-time weekly in dosages of from 1 x 106 to 10 x 106 UT. INF-.alpha. has been administered in combination with chemotherapy, but conflicting results have been reported. The effects of interferon-6 an interferon-y have been studied in RCC, but were found to be inferior to that of INF-.alpha. IL-2 has been administered intravenously in a dose of 25 MIU/m2/8 hours producing a 20% response rate with 7% complete responses. The toxicity was significant due mainly to capillary leak syndrome. Smaller doses of IL-2 are followed by lower responses, but with no significant difference in survival. The subcutaneous administration of IL-2 carries lower toxicity but also a lower response. The co-administration of IL-2 with INF-.alpha. achieved a 38% response rate, but was followed by serious cardiac, hepatic and phychiatric complications. In the most recent studies the above two cytokines were combined with fluorouracil to produce response rates as high as 24-49%, but confirmatory studies are required. The present consensus is that IL-2 combinations are no better than single drug administration which yields 15-20% response rates with long-term remissions in 1/3 of patients who can be considered cured. The newer treatments are based on adoptive cellular immunotherapy either with patient's peripheral lymphocytes or tumor infiltrating lymphocytes which can be induced in vitro with Il-2 and re-administered to the patients. Another type of adoptive treatment is the administration of ***bispecific*** monoclonal antibodies where the one site is linked to a cancer cell while the other carries an immonocyte. The newest therapeutic modalities which have been applied in RCC are gene therapy and cancer ***cell*** ***vaccines*** . In gene therapy, genetic material from cytokines is induced either into tumor cells or into cytotoxic lymphocytes. In both cases a significant amount of cytokines is concentrated in the tumor site. The use of cancer ***cell*** ***vaccines*** with irradiated either autologous or allogeneic tumor

cells is being studied in phase I and II and the preliminary results seem to be encouraging.

L16 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:137621 CAPLUS
DOCUMENT NUMBER: 126:184827
TITLE: Idiotype vaccination strategies against a murine B-cell lymphoma: dendritic cells loaded with idiotype and ***bispecific*** idiotype .times. anti-class II antibodies can protect against tumor growth
AUTHOR(S): Bohlen, Herbert; Thielemanns, Kris; Tesch, Hans; Engert, Andreas; Wolf, H. Juergen; Van Camp, Ben; Urbain, Jacques; Diehl, Volker
CORPORATE SOURCE: Klinik I fur Innere Medizin, Universitat zu Koln, Koln, 50924, Germany
SOURCE: Cytokines Mol. Ther. (1996), 2(4), 231-238
CODEN: CMTHFP; ISSN: 1355-6568
PUBLISHER: Martin Dunitz Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Three strategies were used to evaluate 38C13 B-cell lymphoma-specific idiotype immunization to protect against subsequent lymphoma challenge in C3H/He mice. It was obsd. that tumor-specific immunity could be induced by immunization with (i) KLH-conjugated 38C13 B-cell lymphoma idiotype in complete Freund's adjuvants (survival rate 80%), (ii) dendritic cells pulsed in vitro with native idiotype protein (survival rate 80%), and (iii) ***bispecific*** antibodies composed of B-lymphoma-related idiotype and an MHC class II binding moiety (survival rate 40%). Presentation of idiotype determinants by dendritic cells of ***bispecific*** antibody resulted in lymphoma-specific immunity and obviated the requirement for carrier protein or adjuvant. Moreover, primed dendritic cells induced predominant development of a tumor-specific T-cell response. Each of these immunization strategies resulted in long-term survival without the emergence of idiotype variants or the induction of tumor dormancy.

L16 ANSWER 8 OF 8 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 97154859 MEDLINE
DOCUMENT NUMBER: 97154859
TITLE: Immunogenicity increase of autologous tumor ***cell*** ***vaccines*** by virus infection and attachment of ***bispecific*** antibodies.
AUTHOR: Haas C; Schirrmacher V
CORPORATE SOURCE: German Cancer Research Center, Tumor Immunology, Program (0710), Heidelberg, Germany.
SOURCE: CANCER IMMUNOLOGY, IMMUNOTHERAPY, (1996 Nov) 43 (3) 190-4.
Ref: 41
Journal code: CN3. ISSN: 0340-7004.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199704
ENTRY WEEK: 19970403
AB A new type of cancer vaccine for therapeutic application in cancer patients is described. It consists of three components. (1) autologous tumor cells, (2) Newcastle Disease Virus (NDV), to be used for infection

and (3) ***bispecific*** antibodies (bsAb) which attach to the viral hemagglutinin neuraminidase (HN) molecule on the infected tumor cells. A standardized procedure has been developed for generating virus infected human autologous tumor ***cell*** ***vaccines*** (ATV-NDV) which includes cell dissociation, removal of leukocytes and cell debris, gamma-irradiation and cryopreservation. Infection with the non-virulent strain NDV Ulster is performed within 30 min of co-incubation. While virus infection already increased immunogenicity of the tumor vaccine, further augmentation of T cell stimulatory capacity is achieved by attachment of specially designed bi-specific antibodies (bs HN x CD28 or bs HN x CD3).

L8 ANSWER 1 OF 25 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 2000:227691 CAPLUS
DOCUMENT NUMBER: 132:250020
TITLE: ***Bispecific*** and ***trispecific*** antibodies which specifically react with inducible surface antigens as operational target structures
INVENTOR(S): ***Lindhofer, Horst***
PATENT ASSIGNEE(S): Germany
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000018806	A1	20000406	WO 1999-EP7095	19990922
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
DE 19859110	A1	20000413	DE 1998-19859110	19981221

PRIORITY APPLN. INFO.: DE 1998-19844157 19980925
DE 1998-19859110 19981221

AB According to the invention, an intact ***bispecific*** or ***trispecific*** antibody is provided which comprises at least the following properties: (a) binding to a T cell; (b) binding to at least one antigen on a target cell; (c) binding by the Fc portion thereof (in ***bispecific*** antibodies) or by a third specificity (in ***trispecific*** antibodies). The antigen can be induced and is not found on the target cell in a non-induced state (normal state) or it exists in a low no. that is insufficient to destroy the target cell. The use of these antibodies for immunotherapy of tumors and infections is discussed.

L8 ANSWER 2 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 1
ACCESSION NUMBER: 1999:510768 BIOSIS
DOCUMENT NUMBER: PREV199900510768
TITLE: Method for producing heterologous bi-specific antibodies.
AUTHOR(S): ***Lindhofer, Horst (1)*** ; Thierfelder, Stephan
CORPORATE SOURCE: (1) Munchen West Germany
ASSIGNEE: GSF--Forschungszentrumfur Umweltund Gesundheit
PATENT INFORMATION: US 5945311 Aug. 31, 1999
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Aug. 31, 1999) Vol. 1225, No. 5, pp. NO

PAGINATION.
ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English

L8 ANSWER 3 OF 25 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 1999355457 MEDLINE
DOCUMENT NUMBER: 99355457
TITLE: ***Bispecific*** antibody fragments with CD20 X CD28 specificity allow effective autologous and allogeneic T-cell activation against malignant cells in peripheral blood and bone marrow cultures from patients with B-cell lineage leukemia and lymphoma.
AUTHOR: Brandl M; Grosse-Hovest L; Holler E; ***Kolb H J*** ; Jung G
CORPORATE SOURCE: Department of Hematology and Medical Oncology, Klinikum Grosshadern, University of Munich, Germany.
SOURCE: EXPERIMENTAL HEMATOLOGY, (1999 Aug) 27 (8) 1264-70.
Journal code: EPR. ISSN: 0301-472X.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199910
ENTRY WEEK: 19991003
AB ***Bispecific*** antibodies directed against tumor-associated target antigens and to surface receptors mediating T-cell activation, such as the TCR/CD3 complex and the costimulatory receptor CD28, are capable of mediating T-cell activation resulting in tumor cell killing. In this study, we used the B-cell-associated antigens CD19 and CD20 as target structures on human leukemic cells. We found that a combination of ***bispecific*** antibody fragments (bsFab2) with target x CD3 and target x CD28 specificity induces vigorous autologous T-cell activation and killing of malignant cells in peripheral blood and bone marrow cultures from patients with chronic lymphocytic leukemia and follicular lymphoma. The bsFab2 targeting CD20 were considerably more effective than those binding to CD19. The colony-forming capacity of treated bone marrow was impaired due to large amounts of tumor necrosis factor alpha produced during bsFab2-induced T-cell activation. Neutralizing tumor necrosis factor alpha antibodies were found to reverse this negative effect without affecting T-cell activation and tumor cell killing. CD20 x CD28 bsFab2, when used alone rather than in combination, markedly improved the recognition of leukemic cells by allogeneic T cells. Therefore, these reagents may be capable of enhancing the immunogenicity of leukemic cells in general and, in particular, of increasing the antileukemic activity of allogeneic donor buffy coat cells in relapsed bone marrow transplanted patients.

L8 ANSWER 4 OF 25 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1999343730 MEDLINE
DOCUMENT NUMBER: 99343730
TITLE: Simultaneous activation of T cells and accessory cells by a new class of intact ***bispecific*** antibody results in efficient tumor cell killing.
AUTHOR: ***Zeidler R*** ; Reisbach G; Wollenberg B; Lang S; Chaubal S; Schmitt B; ***Lindhofer H***
CORPORATE SOURCE: Clinical Cooperation Group Bispecific Antibodies,

Department of Otorhinolaryngology, Ludwig-Maximilians-University, Munich, Germany.
SOURCE: JOURNAL OF IMMUNOLOGY, (1999 Aug 1) 163 (3) 1246-52. Journal code: IFB. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199910
ENTRY WEEK: 19991002
AB ***Bispecific*** Abs (bsAb) are promising immunological tools for the elimination of tumor cells in minimal residual disease situations. In principle, they target an Ag on tumor cells and recruit one class of effector cell. Because immune reactions in vivo are more complex and are mediated by different classes of effector cell, we argue that conventional bsAb might not yield optimal immune responses at the tumor site. We therefore constructed a bsAb that combines the two potent effector subclasses mouse IgG2a and rat IgG2b. This ***bispecific*** molecule not only recruits T cells via its one binding arm, but simultaneously activates FcgammaR+ accessory cells via its Fc region. We demonstrate here that the activation of both T lymphocytes and accessory cells leads to production of immunomodulating cytokines like IL-1beta, IL-2, IL-6, IL-12, and DC-CK1. Thus this new class of bsAb elicits excellent antitumor activity in vitro even without the addition of exogenous IL-2, and therefore represents a totally self-supporting system.

L8 ANSWER 5 OF 25 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999316170 EMBASE
TITLE: [Adoptive transfer of malignoma reactive T cells]. ADOPTIVER TRANSFER VON MALIGNOMREAKTIVEN T-ZELLEN.
AUTHOR: Bernhard H.; Meyer zum Buschenfelde Ch.; ***Kolb H.-J.***; Peschel Ch.
CORPORATE SOURCE: Dr. H. Bernhard, III. Medizinische Klinik, Klinikumrechts der Isar, Technische Universitat Munchen, Ismaningerstrasse 22, D-81644 Munchen, Germany. helga.bernhard@tum.ce
SOURCE: Onkologe, (1999) 5/8 (688-694).
Refs: 28
ISSN: 0947-8965 CODEN: ONKOF4
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
LANGUAGE: German

L8 ANSWER 6 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 2000:43330 BIOSIS
DOCUMENT NUMBER: PREV200000043330
TITLE: The generation of monospecific and ***bispecific*** anti-viral cytotoxic T lymphocytes (CTL) for the prophylaxis of patients receiving an allogeneic BMT.
AUTHOR(S): Regn, S. (1); Chen, X. (1); ***Kolb, H.-J. (1)*** ; Roskrow, M. (1)
CORPORATE SOURCE: (1) GSF (National Research Centre for Environment and Health) and Medical Clinic III, Grosshadern University of

Munich, Munich Germany
SOURCE: Blood, (Nov. 15, 1999) Vol. 94, No. 10 SUPPL. 1 PART 1, pp.
154a.
Meeting Info.: Forty-first Annual Meeting of the American Society of Hematology New Orleans, Louisiana, USA December 3-7, 1999 The American Society of Hematology
. ISSN: 0006-4971.
DOCUMENT TYPE: Conference
LANGUAGE: English

L8 ANSWER 7 OF 25 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1999380234 MEDLINE
DOCUMENT NUMBER: 99380234
TITLE: Gene therapy of B-cell lymphoma with cytokine gene-modified
trioma cells.
AUTHOR: Strehl J; Selmayr M; Kremer J P; Hultner L; ***Lindhofer*** ***
H*** ; Mocikat R
CORPORATE SOURCE: GSF-Institut fur Molekulare Immunologie, Munich, Germany.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1999 Sep 24) 83 (1) 113-20.
Journal code: GQU. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199911
ENTRY WEEK: 19991104
AB The trioma approach is a new immunotherapeutic strategy for treating B-cell lymphomas. It is based on converting the tumour idiotype to a ***bispecific*** immunoglobulin that redirects the idiotype to antigen-presenting cells. We show here that even pre-existing tumours can be eradicated by trioma vaccination, that the trioma approach is superior to vaccination with cytokine gene-modified autologous tumour cells and that there is a synergism between trioma immunisation and GM-CSF gene transfer. Furthermore, we show that the immunising potential of GM-CSF gene-modified autologous lymphoma cells is not as dependent on the cytokine expression level as described for other tumour models, such that even minute expression rates are effective. IL-4 gene transfer in the lymphoma model is considerably less efficient or even ineffective when more sensitive systems are used. Remarkably, trioma-mediated effects are extinguished when IL-4 is expressed by the trioma cell. Copyright 1999 Wiley-Liss, Inc.

L8 ANSWER 8 OF 25 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1999:12374 CAPLUS
DOCUMENT NUMBER: 130:51356
TITLE: Method of ex vivo immunizing using heterologous intact
bispecific and/or ***trispecific*** antibodies
INVENTOR(S): ***Lindhofer, Horst*** ; Kolb, Hans-Jochem; ***Zeidler, Reinhard*** ; ***Bornkamm, Georg***
PATENT ASSIGNEE(S): Gsf-Forschungszentrum Fur Umwelt Und Gesundheit, Gmbh,
Germany
SOURCE: Eur. Pat. Appl., 19 pp.
CODEN: EPXXDW

DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 885614	A2	19981223	EP 1998-110972	19980616
EP 885614	A3	19990113		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
DE 19725586	A1	19981224	DE 1997-19725586	19970617
DE 19725586	C2	19990624		
JP 11071288	A2	19990316	JP 1998-170389	19980617
PRIORITY APPLN. INFO.:			DE 1997-19725586	19970617

AB The invention describes a method for ex vivo immunization of human and animal with the following steps: (a) isolation of autologous tumor cells; (b) treatment of tumor cells to prevent their survival after reinfusion; (c) incubation of treated tumor cells with intact heterologous ***bispecific*** and or ***trispecific*** antibodies. The antibodies have the following properties: binding to T-cells, binding to an antigen from the tumor cells, binding through its Fc fragment (by ***bispecific*** antibodies) or through a third specificity (by ***trispecific*** antibodies) to Fc-pos. cells.

L8 ANSWER 9 OF 25 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1998:176147 CAPLUS
DOCUMENT NUMBER: 128:216369
TITLE: Bi- and ***trispecific*** antibodies for induction of tumor immunity
INVENTOR(S): ***Lindhofer, Horst*** ; Kolb, Hans-Jochem; Thierfelder, Stefan
PATENT ASSIGNEE(S): GSF-Forschungszentrum fuer Umwelt und Gesundheit G.m.b.H. Neuherberg, Germany
SOURCE: Ger. Offen., 18 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19710497	A1	19980305	DE 1997-19710497	19970313
DE 19710497	C2	19980709		
DE 19649223	A1	19980305	DE 1996-19649223	19961127
DE 19649223	C2	19980730		
EP 826696	A1	19980304	EP 1997-115190	19970902
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EP 826695	A1	19980304	EP 1997-115188	19970902
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 10179151	A2	19980707	JP 1997-238745	19970903
US 5985276	A	19991116	US 1997-922966	19970903
PRIORITY APPLN. INFO.:			DE 1996-19635743	19960903
			DE 1996-19648976	19961126
			DE 1996-19649223	19961127
			DE 1997-19710497	19970313

AB The invention concerns intact ***bispecific*** or ***trispecific*** antibodies, which can bind simultaneously to the T-cell receptor complex of T-cells, to tumor-assocd. antigens of a tumor cell, and through the Fc fragment of ***bispecific*** antibodies to Fc-receptor pos. cells. The use of these antibodies for induction of tumor immunity in humans and animals is discussed.

L8 ANSWER 10 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1998:150437 BIOSIS
DOCUMENT NUMBER: PREV199800150437
TITLE: A ***bispecific*** antibody induces efficient killing of tumor cells: Phase I-trial in patients with HNSCC.
AUTHOR(S): Wollenberg, B. (1); Schmitt, B. (1); Erndl, S.; Lang, S. (1); ***Lindhofer, H.*** ; Kastenbauer, E. (1); ***Zeidler, R. (1)***
CORPORATE SOURCE: (1) Dep. ENT, LMU, Munich Germany
SOURCE: British Journal of Cancer, (1998) Vol. 77, No. SUPPL. 1, pp. 46.
Meeting Info.: International Symposium on Metastases in Head and Neck Cancer Kiel, Germany January 15-18, 1998
ISSN: 0007-0920.
DOCUMENT TYPE: Conference
LANGUAGE: English

L8 ANSWER 11 OF 25 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.DUPLICATE 5
ACCESSION NUMBER: 1998168459 EMBASE
TITLE: CD22 is a suitable target molecule for detection and high-dose, myeloablative radioimmunotherapy with the monoclonal antibody LL2 in acute lymphatic leukaemia and Waldenstrom's macroglobulinaemia.
AUTHOR: Behr T.M.; Holler E.; Gratz S.; Wormann B.; Sharkey R.M.; Dunn R.M.; Hiddemann W.; ***Kolb H.-J.*** ; Goldenberg D.M.; Becker W.
CORPORATE SOURCE: T.M. Behr, Department of Nuclear Medicine, Georg-August-University of Gottingen, Robert-Koch Str. 40, D-37075 Gottingen, Germany
SOURCE: Tumor Targeting, (1998) 3/1 (32-40).
Refs: 19
ISSN: 1351-8488 CODEN: TUTAF
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 006 Internal Medicine
014 Radiology
025 Hematology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB CD22 is a 135-kD glycoprotein of the immunoglobulin superfamily which is expressed on most B lymphocytes. It has been used successfully as a target molecule for radioimmunodetection and therapy of B-cell non-Hodgkin's lymphoma with the monoclonal antibody CD22 (Mab), LL2. Since CD22 is highly expressed on blasts in acute lymphatic leukaemia of B-cell origin as well as on the malignant lymphocytes of macroglobulinaemia, we studied the potential of LL2 for the detection and therapy of these two haematological malignancies in two pilot cases. A 43-year-old male suffered from macroglobulinaemia, first diagnosed 4 years earlier. The IgM produced by the malignant clone cross-reacted with a ganglioside of

peripheral neurons, causing severe and progressive sensomotor neuropathy. Several bone marrow biopsies as well as a splenectomy were not able to demonstrate the presence of a malignant clone which would be responsible for the IgM production. A localised tumour was suspected, but was not detected by any radiological procedure. Thus, the patient underwent radioimmunodetection (RAID) with 99mTc-LL2 Fab1 (LymphoScan(TM)). The second patient was a 28-year-old male who had common acute lymphatic leukaemia (c-ALL) for 8 years. He had failed 6 high-dose chemotherapy regimens with allogenic bone marrow or stem cell transplantations from his HLA-compatible brother. The patient had also failed two immunotherapeutic approaches with ***bispecific*** murine antibodies, which had caused high titres of HAMA. The patient was treated, with high-dose radioimmunotherapy with 131I-labelled humanised LL2 IgG in myeloablative intention with stem cell support. Although all diagnostic procedures had failed in the macroglobulinaemia patient, 99mTc-LL2 Fab1 showed excellent targeting of widespread parailiac, mediastinal, axillary and cervical lymph node involvement (all smaller than 1 cm in size) as well as a patchy uptake all over the patient's bone marrow as a sign of generalised tumour infiltration, precluding any localised treatment approach, such as external beam irradiation. The c-ALL patient underwent a diagnostic study with humanised LL2 (50 mg of protein, 8 mCi 131I) in order to assess tumour targeting and dosimetry, and was treated based on the result, with 258 mCi hLL2 at the same protein dose. Strong uptake occurred in the patient's bone marrow as well as in several extramedullary tumour sites (lymph nodes, spleen, muscular infiltration of the thigh). At a marrow dose of 30 Gy (whole-body 3.5 Gy, lung 12 Gy), the patient went into complete remission and bone marrow aplasia within two days. Reingraftment of the red marrow took place rapidly. The patient experienced a complete remission lasting for 7 weeks. Relapsed ALL and Waldenstrom's macroglobulinaemia seem to be suitable targets for a radioimmunotherapeutic approach with the anti-CD22 monoclonal antibody, LL2. Future studies will show whether high-dose RAIT with heterologous stem cell support may be able to induce longer-lasting remissions or even be curative in these haematologic malignancies.

L8 ANSWER 12 OF 25 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1997:649115 CAPLUS
DOCUMENT NUMBER: 127:277199
TITLE: Hybridomas of malignant B-cells and antigen presenting cells for use in stimulating an immune response to B-cell neoplasms
INVENTOR(S): Mocikat, Ralf; ***Lindhofer, Horst*** ; Thierfelder, Stefan
PATENT ASSIGNEE(S): GSF - Forschungszentrum fuer Umwelt und Gesundheit Gmbh, Germany
SOURCE: Ger., 6 pp.
CODEN: GWXXAW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19634159	C1	19970925	DE 1996-19634159	19960823
EP 825256	A2	19980225	EP 1997-113697	19970807

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,

IE, FI
JP 10155483 A2 19980616 JP 1997-228536 19970825
US 6007807 A 19991228 US 1997-917216 19970825
PRIORITY APPLN. INFO.: DE 1996-19634159 19960823
AB Hybridomas of malignant B-cells and antigen presenting cells that present bi-specific antibodies to tumor-specific antigens and the cell surface antigens of antigen-presenting cells are described for use in the treatment of B-lymphomas. These hybridomas lead to the formation of tumor-specific T cells. The B-cells are preferably not human (mouse or rat) and the hybridomas are quickly recognized as foreign when injected into the host.

L8 ANSWER 13 OF 25 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 97336010 MEDLINE
DOCUMENT NUMBER: 97336010
TITLE: Trioma-based vaccination against B-cell lymphoma confers long-lasting tumor immunity.
AUTHOR: Mocikat R; Selmayr M; Thierfelder S; ***Lindhofer H***
CORPORATE SOURCE: GSF-Institut fur Immunologie, Munchen, Germany.. mocikat@gsf.de
SOURCE: CANCER RESEARCH, (1997 Jun 15) 57 (12) 2346-9. Journal code: CNF. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199709
ENTRY WEEK: 19970903
AB A major goal of tumor immunotherapy is the induction of a systemic immune response against tumor antigens such as the tumor-specific immunoglobulin idiotype (Id) expressed by lymphomas of the B-cell lineage. We describe an approach based on specific redirection of the tumor Id toward professional antigen-presenting cells (APCs), thereby overcoming the inefficient presentation on the parental transformed B cell. Lymphoma cells are fused to a xenogeneic hybridoma cell line that secretes an antibody against a surface molecule on APCs. Due to preferential assembly between heavy and light chains of antibodies of different species-origin, the resulting "trioma" cells produce at high yield a ***bispecific*** antibody containing the lymphoma Id and the APC-binding arm, which redirects the Id to APCs. Processing and presentation of the Id will lead to T-cell activation. An absolute requirement for inducing a complete tumor protection was the immunization with antibody-secreting trioma cells as a cell-based vaccine instead of the soluble ***bispecific*** antibody. Tumor immunity was specific and long-lasting. Both CD4+ and CD8+ T cells were necessary for inducing tumor immunity.

L8 ANSWER 14 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1997:426558 BIOSIS
DOCUMENT NUMBER: PREV199799725761
TITLE: ***Bispecific*** antibodies effectively purge cancer cells from peripheral blood stem cell collections without affecting colony forming units.
AUTHOR(S): ***Lindhofer, H.*** ; Menzel, H.; Zengerle, U.; ***Zeidler, R.*** ; Chaubal, S.; ***Kolb, H. J.*** ; Thierfelder, S.
CORPORATE SOURCE: GSF Inst. Immunol., Munchen Med. III Klinikum, Grosshadern Germany

SOURCE: Experimental Hematology (Charlottesville), (1997) Vol. 25, No. 8, pp. 879.
Meeting Info.: 26th Annual Meeting of the International Society for Experimental Hematology Cannes, France August 24-28, 1997
ISSN: 0301-472X.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

L8 ANSWER 15 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1997:230396 BIOSIS
DOCUMENT NUMBER: PREV199799529599
TITLE: An intact ***bispecific*** antibody induces activation of T-cells and monocytes/macrophages resulting in efficient killing of tumor cells.
AUTHOR(S): ***Zeidler, R.*** ; Schmitt, B.; Erndl, S.; Lang, S.; Wollenberg, B.; Lindofer, H.
CORPORATE SOURCE: Dep. Otorhinolayngology, Ludwig-Maximilians-Univ., Marchioninistr. 15, D-81377 Munich Germany
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (1997) Vol. 38, No. 0, pp. 29.
Meeting Info.: Eighty-eighth Annual Meeting of the American Association for Cancer Research San Diego, California, USA April 12-16, 1997
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; Abstract
LANGUAGE: English

L8 ANSWER 16 OF 25 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 97131784 MEDLINE
DOCUMENT NUMBER: 97131784
TITLE: ***Bispecific*** antibodies target operationally tumor-specific antigens in two leukemia relapse models.
AUTHOR: ***Lindhofer H*** ; Menzel H; Gunther W; Hultner L; Thierfelder S
CORPORATE SOURCE: Forschungszentrum fur Umwelt und Gesundheit (GSF)-Institut fur Immunologie, Munich, Germany.
SOURCE: BLOOD, (1996 Dec 15) 88 (12) 4651-8.
Journal code: A8G. ISSN: 0006-4971.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199704
ENTRY WEEK: 19970402
AB Despite improved procedures in chemotherapy and bone marrow transplantation (BMT), post-BMT leukemia relapse rates have remained rather constant in the last decade. Immunotherapy with monoclonal or ***bispecific*** antibodies (bsAb) is a promising approach to improve this situation, but is hampered by the absence of tumor-specific antigens on the majority of tumors. To evade this problem, we developed a new tumor-specific approach in which ***bispecific*** antibodies exploit chimerism after allogeneic BMT by redirecting donor T cells against recipient-specific antigens on tumor cells. Two different leukemia relapse models were established using a T-cell lymphoma (ST-1) and a B-cell

lymphoma (BCL1) to evaluate the efficiency of such a therapy. In these experiments, irradiated BALB/c (Thy-1.2+, I-Ad) mice were transplanted with C57BL/6 Thy-1.1 (I-Ab) BM cells under the protection of graft-versus-host disease-preventing monoclonal antibodies. Forty-five days after BMT, the chimeric mice were injected with either 2 x 10(4) recipient-type, Thy-1.2+, CD3- ST-1 cells or major histocompatability complex (MHC) class II+ (I-Ad)-BCL1 cells. Four days later, the mice were treated with 8 microg bsAb G2 (anti-CD3 x anti-Thy-1.2) or 10 microg (+10 microg, day 6) bsAb BiC (anti-CD3 x anti-I-Ad), respectively. These combinations guaranteed exclusive binding of the bsAbs target arms to tumor cells, leaving the surrounding, donor-type hematopoietic cells unbound. Compared with the parental antibodies, the bsAbs markedly reduced tumor mortality. Between 34% and 83% of mice survived in the bsAb groups compared with 0% of the control groups treated with parental antibodies, clearly documenting the benefit of the redirection principle. Furthermore, cytokine release (interleukin-6) after anti-CD3 antibody or bsAb treatment was decreased by administering a low-dose antibody preinjection. We have shown (1) that 6 weeks after BMT, when donor T-cell reconstitution is still in progress, T-cell-redirecting bsAb are clearly superior to parental antibodies in terms of tumor cell elimination; and (2) that the polymorphism of a common antigen such as Thy-1 or a clinically more relevant target antigen such as MHC class II can be used as an operational tumor-specific antigen after allogeneic BMT.

L8 ANSWER 17 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1996:450856 BIOSIS
DOCUMENT NUMBER: PREV199699173212
TITLE: Increased tumor-specificity and -elimination by selectively binding ***bispecific*** antibodies in vivo.
AUTHOR(S): ***Lindhofer, H.*** ; Mysliwietz, J.; Thierfelder, S.
CORPORATE SOURCE: GSF-Inst. Immunol., Muenchen Germany
SOURCE: Experimental Hematology (Charlottesville), (1996) Vol. 24, No. 9, pp. 1090.
Meeting Info.: 25th Annual Meeting of the International Society for Experimental Hematology New York, New York, USA
August 23-27, 1996
ISSN: 0301-472X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L8 ANSWER 18 OF 25 CAPLUS COPYRIGHT 2000 ACS
ACCESSION NUMBER: 1995:498513 CAPLUS
DOCUMENT NUMBER: 122:237782
TITLE: Process for producing heterologous ***bispecific*** antibodies
INVENTOR(S): ***Lindhofer, Horst*** ; Thiefelder, Stefan
PATENT ASSIGNEE(S): GSF = Forschungszentrum fuer Umwelt und gesundheit GmbH, Germany
SOURCE: Ger., 10 pp.
CODEN: GWXXAW
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 4419399	C1	19950309	DE 1994-4419399	19940603
WO 9533844	A1	19951214	WO 1995-EP1850	19950516
W: CA, JP, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 763128	A1	19970319	EP 1995-919458	19950516
EP 763128	B1	19991201		
R: AT, BE, CH, DE, DK, FR, GB, IT, LI, NL, SE				
JP 09506001	T2	19970617	JP 1995-500228	19950516
AT 187176	E	19991215	AT 1995-919458	19950516
US 5945311	A	19990831	US 1996-758430	19961129
PRIORITY APPLN. INFO.:			DE 1994-4419399	19940603
			WO 1995-EP1850	19950516

AB A process is described for producing heterologous ***bispecific*** IgG antibodies, or quadromas, from 2 fused hybridomas. One of the hybridomas produces antibodies with an affinity for protein A, and the other produces antibodies with little or no affinity for protein A. Thus, a quadroma was produced which included an anti-mouse CD3 rat antibody of the IgG2b subclass, and an anti-mouse Thy-1.2 mouse antibody of the IgG2a subclass.

L8 ANSWER 19 OF 25 MEDLINE DUPLICATE 8

ACCESSION NUMBER: 95394030 MEDLINE
DOCUMENT NUMBER: 95394030
TITLE: Immunosuppression by Fc region-mismatched anti-T cell antibody treatment.
AUTHOR: Thierfelder S; Mocikat R; Mysliwietz J; ***Lindhofer H*** ; Kremmer E
CORPORATE SOURCE: GSF-Forschungszentrum fur Umwelt und Gesundheit, Institut fur Immunologie, Munich, Germany..
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1995 Aug) 25 (8) 2242-6. Journal code: EN5. ISSN: 0014-2980.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199512

AB Formation of anti-antibodies (anti-Ab) is known to counteract immunotherapy with anti-T cell antibodies. Our previously described immunological approach prevented anti-Ab with the consequence of prolonged survival of fully mismatched skin grafts in C57BL/6 mice. These mice were treated with a single priming injection of a monoclonal anti-T cell Ab followed by repeated injections of anti-T cell mAb differing in species origin from the priming mAb. We now show prolonged tolerance to discordant xenogeneic, to ***bispecific*** , and even to polyclonal Ab, and demonstrate that the underlying immunosuppressive principle is due to a difference in heavy chain constant region between first and second antibodies, independent of whether or not they share the same idiotype. To examine this phenomenon, a panel of mAb was generated which share the same mouse anti-Thy-1.2 idiotype, but carry a human IgG1(T23), IgG3(T212C8), or

mouse IgG2a(MmT1) constant heavy chain region. We found that sequential injection of MmT1 and T23 according to the above treatment schedule induced huIgG1 isotype-specific tolerance to T23, which was similar to that seen when using a primary mAb (MmT5) that was, instead, fully mismatched with T23 in both idiotype and constant region. Thus, differences of idiotype between primary and booster Ab were inconsequential for their ability to inhibit anti-Ab formation. This novel form of induced specific tolerance to anti-T cell Ig survived graft rejection and was still evident 230 days after termination of the T cell depletion protocol. Taken together, these results demonstrate that rechallenge with Fc region-mismatched Ab opens an immunological window that allows for induction of tolerance to immunogenic anti-T cell Ab and prolonged immunosuppression.

L8 ANSWER 20 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1995:424064 BIOSIS
DOCUMENT NUMBER: PREV199598438364
TITLE: Leukemia relapse after aBMT: ***Bispecific*** antibodies target operationally tumor-specific antigens.
AUTHOR(S): ***Lindhofer, H.*** ; Menzel, H.; Thierfelder, S.
CORPORATE SOURCE: GSF-Inst. Immunol., Muenchen Germany
SOURCE: Experimental Hematology (Charlottesville), (1995) Vol. 23, No. 8, pp. 788.
Meeting Info.: 24th Annual Meeting of the International Society for Experimental Hematology Duesseldorf, Germany August 27-31, 1995
ISSN: 0301-472X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L8 ANSWER 21 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1995:383349 BIOSIS
DOCUMENT NUMBER: PREV199598397649
TITLE: Generation of ***bispecific*** Ab-fragments for targeting T cell mediated lysis of tumor cells in a mouse lymphoma model.
AUTHOR(S): Bauer, Konrad (1); ***Lindhofer, Horst (1)*** ; Plueckthun, Andreas; Mocikat, Ralph (1)
CORPORATE SOURCE: (1) GSF-Inst. Immunol., Marchionistr. 25, D-81377 Muenchen Germany
SOURCE: 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY.. (1995) pp. 464. The 9th International Congress of Immunology.
Publisher: 9th International Congress of Immunology San Francisco, California, USA.
Meeting Info.: Meeting Sponsored by the American Association of Immunologists and the International Union of Immunological Societies San Francisco, California, USA July 23-29, 1995
DOCUMENT TYPE: Conference
LANGUAGE: English

L8 ANSWER 22 OF 25 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 95325592 MEDLINE
DOCUMENT NUMBER: 95325592
TITLE: Preferential species-restricted heavy/light chain pairing in rat/mouse quadromas. Implications for a single-step purification of ***bispecific*** antibodies.

AUTHOR: ***Lindhofer H*** ; Mocikat R; Steipe B; Thierfelder S
CORPORATE SOURCE: GSF, Immunology Institute, Munich, Germany..
SOURCE: JOURNAL OF IMMUNOLOGY, (1995 Jul 1) 155 (1) 219-25.
Journal code: IFB. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals
ENTRY MONTH: 199510

AB Conventional mouse/mouse or rat/rat hybrid-hybridoma supernatants contain up to 10 different IgG molecules consisting of various combinations of heavy and light chains. Hence, the yield of functional ***bispecific*** Ab is low, and purification is often complicated, hampering a general preclinical evaluation of, e.g., ***bispecific*** Ab-mediated tumor immunotherapy in animal models. In experiments to overcome this drawback we found that fusion of rat with mouse hybridomas opens the possibility of large scale production of ***bispecific*** Ab due to the increased incidence of correctly paired Ab and facilitated purification. In essence, rat/mouse quadroma-derived ***bispecific*** Ab have the following advantages: 1) enrichment of functional ***bispecific*** Ab because of preferential species-restricted heavy/light chain pairing (observed in four of four rat-mouse quadromas) in contrast to the random pairing in conventional mouse/mouse or rat/rat quadromas, and 2) a possible one-step purification of the quadroma supernatant with protein A. This simple chromatography step does not bind unwanted variants with parental rat/rat heavy chain configuration, and the desired rat/mouse ***bispecific*** Ab are retained, which can then easily be separated from parental mouse Ab by sequential pH elution.

L8 ANSWER 23 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1995:362606 BIOSIS
DOCUMENT NUMBER: PREV199598376906
TITLE: Preferential species-restricted heavy/light chain pairing in rat/mouse quadromas: Implications for a single-step purification of ***bispecific*** antibodies.
AUTHOR(S): ***Lindhofer, Horst*** ; Mocikat, Ralph; Steipe, Boris; Thierfelder, Stefan (1)
CORPORATE SOURCE: (1) GSF-Inst. Immunologie, Marchioninistr. 25, 81377 Munich
Germany
SOURCE: Journal of Immunology, (1995) Vol. 155, No. 1, pp. 218-225.
ISSN: 0022-1767.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Conventional mouse/mouse or rat/rat hybrid-hybridoma supernatants contain up to 10 different IgG molecules consisting of various combinations of heavy and light chains. Hence, the yield of functional ***bispecific*** Ab is low, and purification is often complicated, hampering a general preclinical evaluation of, e.g., ***bispecific*** Ab-mediated tumor immunotherapy in animal models. In experiments to overcome this drawback we found that fusion of rat with mouse hybridomas opens the possibility of large scale production of ***bispecific*** Ab due to the increased incidence of correctly paired Ab and facilitated purification. In

essence,
rat/mouse quadroma-derived ***bispecific*** Ab have the following advantages: 1) enrichment of functional ***bispecific*** Ab because of
preferential species-restricted heavy/light chain pairing (observed in four of four rat-mouse quadromas) in contrast to the random pairing in conventional mouse/mouse or rat/rat quadromas, and 2) a possible one-step purification of the quadroma supernatant with protein A. This simple chromatography step does not bind unwanted variants with parental rat/rat heavy chain configuration, and the desired rat/mouse ***bispecific*** Ab are retained, which can then easily be separated from parental mouse Ab
by sequential pH elution.

L8 ANSWER 24 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1994:468541 BIOSIS
DOCUMENT NUMBER: PREV199497481541
TITLE: Rat-mouse quadromas allow augmented generation of ***bispecific*** antibodies and single step purification:
First in vivo studies.
AUTHOR(S): ***Lindhofer, H.*** ; Menzel, H.; Thierfelder, S.
CORPORATE SOURCE: GSF-Inst. Immunologie, Munich Germany
SOURCE: Experimental Hematology (Charlottesville), (1994) Vol. 22, No. 8, pp. 763.
Meeting Info.: 23rd Annual Meeting of the International Society for Experimental Hematology Minneapolis, Minnesota,
USA August 21-25, 1994
ISSN: 0301-472X.
DOCUMENT TYPE: Conference
LANGUAGE: English

L8 ANSWER 25 OF 25 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1995:47142 BIOSIS
DOCUMENT NUMBER: PREV199598061442
TITLE: Preferential species-restricted heavy/light chain pairing in rat/mouse quadromas detected during single step purification of ***bispecific*** antibodies on protein A.
AUTHOR(S): ***Lindhofer, H.*** ; Mocikat, R.; Thierfelder, S.
CORPORATE SOURCE: Inst. Immunol., Muenchen Germany
SOURCE: Immunobiology, (1994) Vol. 191, No. 2-3, pp. 248.
Meeting Info.: XXVth Meeting of the Society of Immunology Konstanz, Germany September 21-24, 1994
ISSN: 0171-2985.
DOCUMENT TYPE: Conference
LANGUAGE: English

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3	L3	3	lindhofer$.in.
4	L4	20	kolb-h$.in.
5	L5	4	zeidler-r$.in.
6	L6	2	bornkamm-g$.in.
7	L7	28	3 or 4 or 5 or 6
8	L8	152	424/277.1.ccls.
9	L9	4066	autologous
10	L10	65	9 and 8
11	L13	63	424/136.1.ccls.